DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's payment and submission filed 3/9/2011, has been received and entered into the present application. Accordingly, prosecution has been reopened.

The declaration of Frank Cuttitta under 37 C.F.R. 1.132 filed on 4/28/2011 has been received.

Applicant's amendment 3/9/2011 has been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Status of Claims

Claims 80-81, 90-97 and 100-108 are pending.

Claims 91-97 are withdrawn. Claims 92-97 are newly withdrawn for being dependent from a withdrawn claim.

Claims 80-81, 90 and 100-108 are currently under examination and the subject matter of the present Office Action.

Maintained rejections:

Claim Rejections - 35 USC § 102

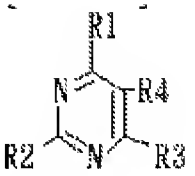
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 80-81, 90 and 100-108 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 10212235 (original document and translation are attached) as evidenced by the National Cancer Institute (1/28/2005) and Patel et al. (Biochimica et a Biophysica Acta, 1766, 2006: 23-41).

JP 10212235 teaches a compound of formula (I) wherein the compound is that of instant claim 80 (paragraph [0064] of translation):



[I]

化合物番号	R1	R2	R3	R4
105	Cl	-NH2	-NHCH2CH2OH	H

Further, it is taught that the compounds of formula (I) is effective for the treatment of tumors, for example, stomach cancer, such as malignant tumor, a benign tumor, and a precancerous change, lung cancer, hepatoma, a pancreatic cancer, colon cancer, a malignant lymphoma, leukemia, a breast carcinoma, melanoma, renal cancer, brain tumor, peritoneal tumor, spinal cord tumor, hypophyseal tumor, thyroid tumor, laryngeal cancer etc. (paragraph [0035] of translation).

Thus, while the prior art does not explicitly teach that lung cancer, hepatoma, a pancreatic cancer, colon cancer, a malignant lymphoma, leukemia, a breast carcinoma, melanoma, renal cancer, brain tumor, peritoneal tumor, spinal cord tumor, hypophyseal tumor, thyroid tumor, laryngeal cancer etc. aberrantly expresses GRP, the claimed limitation does not appear to result in a manipulative difference because as

evidenced by Patel et al. teach that GRP is known to be over expressed in many tumors including lung, prostate, breast, stomach, pancreas and colon (abstract). Thus, the claimed cancers, e.g., patient population, appears to be the same as the prior art. Applicants are reminded that the office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed patient population is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). In the instant case, it should be noted that the present claims do not require any detection or measuring of GRP overexpression. In contrast, the claims require that the patient have a cancer which aberrantly expresses GRP which as evidenced by Patel et al. (above), many tumors including lung, prostate, breast, stomach, pancreas and colon over expresses GRP. As such, the selecting step appears to be met.

Though JP 10212235 is silent as to the effect of the elected compound to inhibit an activity of aberrant gastrin releasing peptide (GRP), the administration of the claimed compound to patients suffering from cellular proliferative disorders is expected to necessarily have the claimed effect of inhibiting an activity of aberrant GRP, whether recognized by the author or not. Products of identical chemical composition cannot exert mutually exclusive properties when administered under the same circumstance or, in the present case, the same host. Please reference MPEP 2112.

Moreover, the very teaching of administering the identical compound to the same patient populations (i.e. patients suffering from cellular proliferative disorders) necessarily means that the claimed inhibition of aberrant GRP is necessarily present, whether recognized by the author or not. Further, the treatment of a tumors would necessarily inhibit angiogenesis since angiogenesis is responsible for the progression of the disease (i.e. is angiogenesis mediated), per National Cancer

Institute. As stated supra, products of identical composition cannot exert mutually exclusive properties. Please reference MPEP 2112 and *Ex parte Novitski*, 26 USPQ 1389 (Bd. Pat. App. and Inter 1993).

Response to Applicant's Remarks

Applicant alleges that claim 90 has been amended to recite a step of selecting a subject.

This is not the case. Instant claim 90 recites: a method of inhibiting an aberrant activity of a gastrin releasing peptide (GRP), comprising: contacting the peptide with an effective amount of a pharmaceutical composition comprising a compound of formula XV'. **It is emphasized that the claims do not require a method step of actually measuring or detecting GRP activity and administering to a patient who overexpresses and underexpresses GRP said compound.**

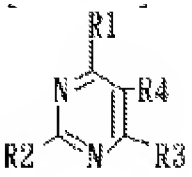
Declarant alleges that one would not assume in the absence of experimental evidence that the compounds provide for an anti-angiogenic effect. In support of the allegations, Exhibit BB (Hanahan et al.) and Exhibit CC (Butowski et al.). It appears Applicant has cited the above articles in support that angiogenesis is not responsible for the progression of tumors. In other words that tumors are not angiogenesis mediated. Firstly, it should be noted that Applicant is guided to MPEP 716.0(c)III which states: "In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). With regard to the references, neither of the references appear to teach that tumors are not angiogenesis mediated. Applicant and Declarant guide the Examiner to the table on page 118 in support that "an effective antitumor-therapy might inhibit proliferation without tumor cell proliferation." This does not appear to be the case. The table on page 118 lists selected small molecule targeted agents being studied in patients with glioma. In fact, the article teaches "angiogenesis is vital to tumor growth

and is a key feature in pathologic diagnosis of GBM." (page 120, column 2, last paragraph). Further, Hanahan teaches that "the importance of angiogenesis for the growth of solid tumors is now well recognized" (page 353, bridging paragraphs). Therefore, Applicants and Declarants contention that the treatment of tumors would not inhibit angiogenesis is not found persuasive. Both of Applicants own cited articles teach that angiogenesis is vital and well recognized for the progression of tumor growth, and as such if anything support the evidentiary article (National Cancer Institute) already made of record.

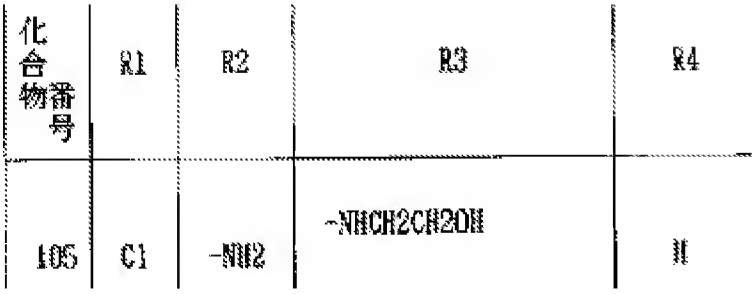
Applicant and Declarant allege that the results presented in JP10212235 are drawn to an in vitro effect on proliferation of 54 different cancer cells lines and no angiogenesis effect was tested. Again, as stated above, the cited evidentiary reference as well as Applicant's own cited reference provide support that the treatment of a tumors would necessarily inhibit angiogenesis since angiogenesis is responsible for the progression of the disease (i.e. is angiogenesis mediated)

Applicant and Declarant allege that the results demonstrate considerable variable and that the antiproliferative effect of every species of compound cannot be assumed. JP 10212235 clearly states that compounds of formula (I), including the elected compound, are useful for the treatment of tumors, for example, stomach cancer, such as malignant tumor, a benign tumor, and a precancerous change, lung cancer, hepatoma, a pancreatic cancer, colon cancer, a malignant lymphoma, leukemia, a breast carcinoma, melanoma, renal cancer, brain tumor, peritoneal tumor, spinal cord tumor, hypophyseal tumor, thyroid tumor, laryngeal cancer etc. (paragraph [0035] of translation).

Though Applicant and Declarant allege that one of skill would not make the same inference about Compound I and its specie that can be made about Compound 77427. Applicant is reminded that JP10212235 specifically envisage the instantly claimed compound:



[I]



Applicant and Declarant allege that the second set of experiments involves administration of Compound 44 to a leukemia cell line. Declarant concludes (1) an in vivo measurement on cell proliferation has not been made and (2) "compound 44 has some anti-cancer effect but without additional data this effect cannot be defined." This is not found persuasive. It is not clear what Applicant regards "as additional data" which is necessary.

Applicant and Declarant allege that the structures of compounds tested in JP10212235 are structurally different from Compound 105. This is not found persuasive. Firstly, it should be noted that JP10212235 specifically states that the compounds of formula (I), including the elected compound, are useful for the treatment of tumors, for example, stomach cancer, such as a malignant tumor, a benign tumor, and a precancerous change, lung cancer, hepatoma, pancreatic cancer, colon cancer, malignant lymphoma, leukemia, breast carcinoma, melanoma, renal cancer, brain tumor, peritoneal tumor, spinal cord tumor, hypophyseal tumor, thyroid tumor, laryngeal cancer (paragraph [0035] of translation). With regard to the Exhibit DD, it should be noted that it only exhibits a fraction of the one hundred and thirty one compounds tested. Therefore, the list set forth by Applicant is not representative of the compounds actually tested by the reference. Arguendo the above, Applicant has not set forth any reasoning or evidence as to what these "structural differences" are and why they do not necessarily infer a "biological property." Applicant fails to advanced any specific reasons or evidence, aside from Counsel's own allegation, in support of this position that no motivation exists in the present obviousness rejection. This assertion by Counsel is an unsupported allegation and fails to take the place of evidence in the record. Statements of this nature are clearly unpersuasive in accordance with the guidance provided at MPEP

2145, which states "The arguments of counsel cannot take the place of evidence in the record."

Applicant alleges that the claim has been amended to recite a method of inhibiting aberrant GRP activity. It is not clear how Applicant has concluded that this amendment furthers prosecution. As stated in the rejection, the very teaching of administering the identical compound to the same patient populations (i.e. patients suffering from cellular proliferative disorders) necessarily means that the claimed inhibition of GRP (whether aberrant or not) is necessarily present, whether recognized by the author or not. Applicant has failed to show evidence to the contrary.

Applicant and Declarant cite the Moody et al. reference in support that "only 42 percent of small cell lung cancer and 32 percent of non-small cell lung cancer cell lines tested express the GRP receptor." This is erroneous. Moody et al. specifically states "Table I shows that 42 percent of the SCLC cell lines and 32 percent of NSLC cell lines examined bound **with high affinity**" (emphasis added). Moody et al. does NOT teach that GRP was not present. The sentence after this states "These data indicate that moderate densities of **GRP receptors are present** in both SCLC and NSCLC cell lines..." (page 240, column 1, paragraph 3). Moody et al. in fact concludes that "In summary these data indicate that GRP receptors are biologically active in NSCLC cells" (page 255, column 2). The statements and conclusion found in Moody et al. are clearly in stark contrast to Applicant's allegations.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 7am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/

Supervisory Patent Examiner, Art Unit 1628